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Formal Ir-Catalyzed Ligand-Enabled Ortho and Meta Borylation of Aromatic Aldehydes via in Situ-Generated Imines

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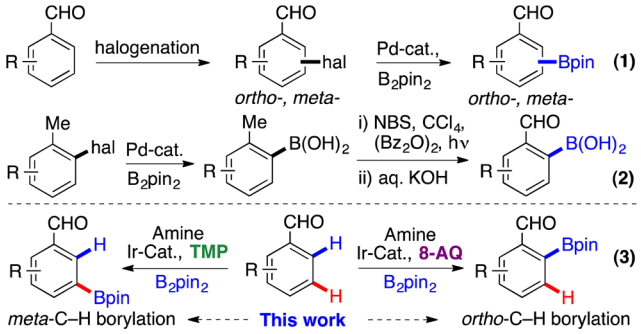
Supporting Information

ABSTRACT: The ligand-enabled development of ortho and meta C−H borylation of aromatic aldehydes is reported. It was envisaged that while ortho borylation could be achieved using *tert*-butylamine as the traceless protecting/directing group, meta borylation proceeds via an electrostatic interaction and a secondary interaction between the ligand of the catalyst and the substrate. These ligand−substrate electrostatic interactions and secondary B−N interactions provide an unprecedented controlling factor for meta-selective C−H activation/borylation.

Over the past decade, C−H bond functionalizations have attracted extensive attention as competent and ideal reactions.[1] From this perspective, C−H bond borylation has shown potential because of the synthetic versatility for which B−C bonds are well-known. A major challenge in C−H borylations is how to control the selectivity. Generally, steric effects often govern the regioselectivity of aromatics,[2] making C−H borylations complementary to widely used directed ortho metalations (DoMs).[3] However, the inherent functional group restriction and practical limitations of DoMs (e.g., groups like esters are incompatible with DoM and require low temperature) have strengthened efforts to develop efficient method for ortho C−H borylations. In this context, few methods for the functional-group-directed[4] ortho borylations[5] have been developed.

On the other hand, meta-selective C−H bond borylation of arenes remains a great challenge. The development of strategy for meta-selective C−H bond borylation is very difficult. Literature reports revealed that only one type of meta C−H borylation is available, that by Smith and Maleczka[6] and Hartwig[7] from 1,3-disubstituted arenes. The regiochemistry of this meta borylation results mainly from sterics.[8] Despite the broad utility of this sterically controlled meta borylation, the chemistry is limited mostly to 1,3-disubstituted arenes. Moreover, arenes bearing reactive functional groups such as aldehydes, ketones, etc. are not well tolerated.[9] Notably, when this Communication was in preparation, a paper describing a novel concept of a meta-selective C−H borylation by a secondary interaction between the ligand and the substrate appeared.[10] Unarguably, this method is one of the most efficient approaches toward meta borylation. However, there are many unsolved problems for the meta borylation. Thus, a critical challenge in developing these catalytic processes is the selective ortho and meta borylation of benzaldehydes. Traditionally, ortho- and meta-borylated benzaldehydes were prepared via halogenation of benzaldehydes followed by a Miyaura cross-coupling reaction with bis-(pinacolato)diborane (eqs 1 and 2).[11,12] Herein we report the



discovery of a one-pot unified strategy for ortho- and meta-selective C−H borylations of benzaldehydes using ligand-enabled iridium-catalyzed C−H activation (eq 3).

Recently, Fernández-Lassaletta,[13] Sawamura,[14] and Ishiyama[15] disclosed an elegant nitrogen-directed ortho borylation of 2-phenylpyridines and hydrazones. Inspired by these results, we hypothesized that imines may serve as an easily removable directing group[16] for ortho borylation of benzaldehydes. To test this hypothesis, benzaldehyde-derived imines were treated with B_2pin_2 under the standard borylation conditions using hydrazone-derived ligand **L1** developed by Fernández and Lassaletta[13a] (Table 1, entry 1). While no borylation was observed for the methyl and isopropyl imines, the *tert*-butyl imine gave good ortho selectivity (86%; entry 4).[17] Notably, when the crude reaction mixtures were monitored by GC/MS, the products appeared as aldehyde-borylated products.[18] Gratifyingly, the combination of *tert*-butylamine, 8-AQ, and B_2pin_2 was found to be the best borylation conditions, giving 100% ortho selectivity and an excellent isolated yield (87%) (entry 6). Notably, methylamine provided only 7% yield using 8-AQ as the ligand system (entry 7), presumably because the methyl imine is incapable of opening a vacant coordination site in order to undergo the ortho borylation because of the lower steric bulk compared with the *tert*-butyl imine.[19] Other ligand systems such as **L2**, **L3**, and **L4** were less effective than the 8-AQ ligand system (entries 8−10).

With these promising results in hand, borylations for a range of aldehydes were executed, and the results are shown in Table 2.

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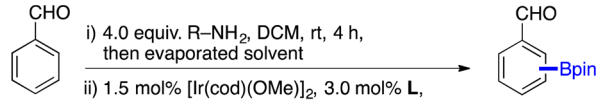
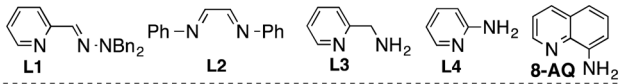
Table 1. Evaluation and Optimization of the Reaction Conditions[a]



#	R	Ligand (L)	B-source	Ratio (o/m/p) [b]	Yield (%)
1	Me	L1	B_2pin_2 (0.7 eq.)	–	0
2	^{i}Pr	L1	B_2pin_2 (0.7 eq.)	–	0
3	^{t}Bu	L1	HBpin (1.5 eq.)	33/37/30	53
4	^{t}Bu	L1	B_2pin_2 (0.7 eq.)	86/8/6	57 [c]
5	^{t}Bu	8-AQ	HBpin (1.5 eq.)	–	0
6	^{t}Bu	8-AQ	B_2pin_2 (0.7 eq.)	100/0/0	87 [d]
7	Me	8-AQ	B_2pin_2 (0.7 eq.)	100/0/0	7
8	^{t}Bu	L2	B_2pin_2 (0.7 eq.)	100/0/0	66 [e]
9	^{t}Bu	L3	B_2pin_2 (0.7 eq.)	95/3/2	72 [f]
10	^{t}Bu	L4	B_2pin_2 (0.7 eq.)	97/2/1	62 [g]

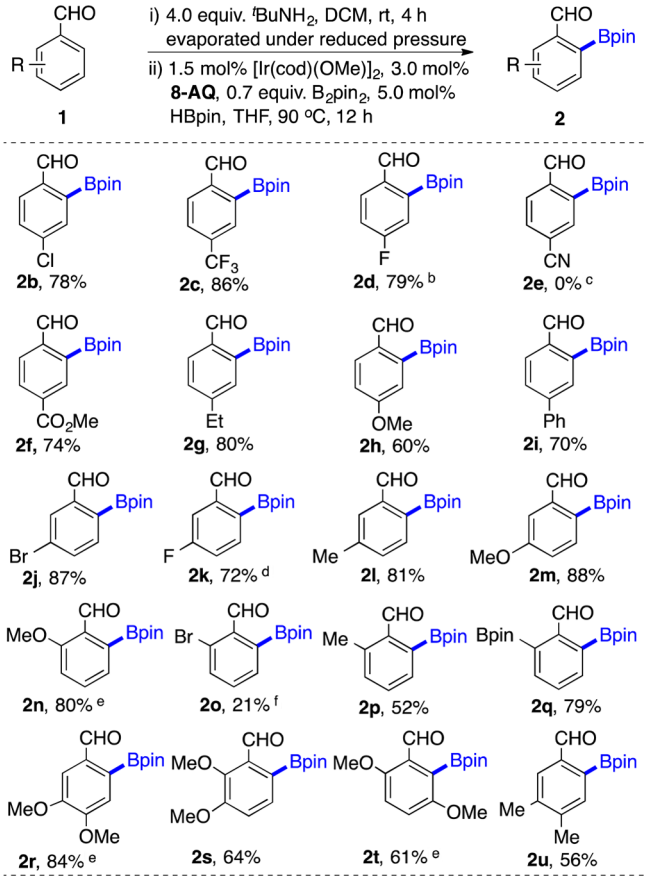


[a]Reactions were run with 1.0 mmol of substrate, and yields are for isolated ortho isomers after column chromatography. [b]Ratios were calculated by GC-FID analysis of the crude reaction mixtures. In GC/MS no imine-borylated products were found; only aldehyde-borylated products were observed. [c]Mono/*o*,*o*-di = 90/10. [d]Mono/*o*,*o*-di = 89/11. [e]Mono/*o*,*o*-di = 80/20. [f]Mono/*o*,*o*-di = 87/13. [g]Mono/*o*,*o*-di = 85/15.

The reactions were conducted under identical conditions, and the reaction times were not optimized. It was found that diverse substituents such as halogens (Cl, F, Br), alkyl groups (Me, Et, CF_3), phenyl, and methoxy were tolerated well under these borylation conditions. Irrespective of the substituent present in the aryl ring, 4-substituted benzaldehydes smoothly underwent C−H borylations to afford the ortho-directed products in good to excellent yields without any diborylations (entries **2b−d** and **2f−i**), except for entry **2d**, which resulted in 7% meta isomer. However, 4-cyanobenzaldehyde failed to undergo C−H borylation (entry **2e**). Employment of other ligand systems such as **L1**, **L2**, **L3**, and **L4** was also unsuccessful (see the Supporting Information (SI) for details). Remarkably, for borylation of 4-phenylbenzaldehyde, the Ph C−H bonds are unperturbed under the borylation conditions, producing exclusively the ortho-directed product (entry **2i**). Notably, meta-substituted benzaldehydes (entries **2j−m**) reacted regioselectively at the sterically less impeded C−H site. In the case of 3-fluorobenzaldehyde, though the expected borylation position is the most acidic proton, flanked by CHO and F, it did not undergo borylation exclusively (25% borylation) under these reaction conditions (entry **2k**). Instead, borylation occurred at the other ortho proton, which is less acidic. Next, we studied the scope of 2-substituted substrates. It was found that both electron-rich and electron-poor substituents are very efficient in these C−H borylations, giving exclusively ortho products (entries **2n**, **2p**, and **2q**). However, 2-bromobenzaldehyde borylation was not good (21% conversion; entry **2o**). Furthermore, we have shown that these borylations can be successfully employed to a range of highly electron-rich and differently substituted benzaldehydes (entries **2r−u**).

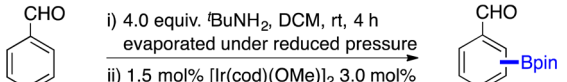
Next, we focused on the ligand screening for the meta-selective C−H activation/borylation. We chose benzaldehyde as our model system, and borylation was performed with bipyridines **L5−L7**. As shown in Table 3, there is a clear indication of increasing meta selectivity as the bipyridine ligand is made more electron-rich (entries 1−3). Encouraged by these initial results,

Table 2. Ortho Borylation of Substituted Benzaldehydes[a]

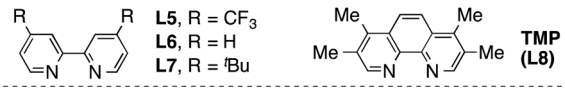


[a]Reactions were run with 1.0 mmol of substrate, and yields are for isolated aldehyde-borylated products after column chromatography. [b]Ortho/meta = 93/07. [c]No reaction occurred even with ligand **L1**. [d]ortho/ortho = 75/25. [e]Reactions were conducted using ligand **L1**. [f]21% conversion; the product could not be isolated because of rapid protodeborylation.

Table 3. Ligand Screening for Meta Borylation[a]



#	L	(meta/para/ortho)[b]	mono/di	Conversion (%)[c]
1	**L5**	11/61/28	89/11	63
2	**L6**	33/46/21	82/18	83
3	**L7**	47/37/16	88/12	88
4	**L8**	66/23/11	97/03	93 (67)[d]



[a]Reactions were run with 1.0 mmol of substrate. [b]GC ratios. [c]GC conversion was measured using dodecane as an internal standard. [d]The isolated yield of the meta-borylated aldehyde product is given in parentheses.

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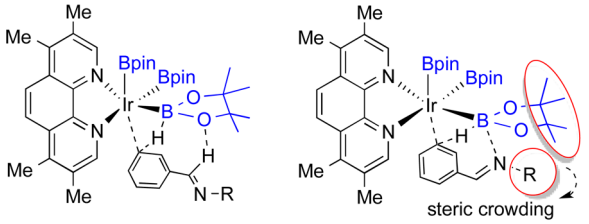
we next attempted borylation using TMP (**L8**) as the ligand. To our delight, improved meta selectivity (66% meta-borylated aldehyde product) was observed with excellent conversion (entry 4). To find out the origin of the increased selectivity, we hypothesized that two important factors might play significant roles: (i) an electrostatic interaction[20] arising from the encapsulation[21] by the tris(boryl)iridium complex attached with the electron-rich ligand and imine substrate and (ii) a secondary interaction of the substrate via either H-bonding[22] between the imine hydrogen atom and the boryl oxygen atom of the catalyst (Chart 1, **TS-1**) or an interaction between the imine N atom and the boryl B atom of the catalyst (**TS-2**).

Chart 1. Hypothesis for the Origin of Meta Selectivity

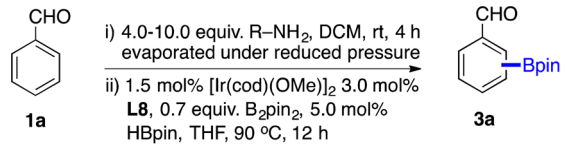


TS-1: H Bond Directed **Ts-2: B–N Bond Directed**

As the electrostatic interaction that enhances the meta selectivity is present in both cases (**TS-1** and **TS-2**), the question of which transition state (**TS-1** or **TS-2**) actually controls the meta selectivity still remains. In the case of the H-bond-directed approach (**TS-1**), the imine substituent (R) is far away from the reaction center, and thus, the outcome of the meta borylation should not be dependent on the size of the R group. On the other hand, in the case of **TS-2**, the outcome should be affected by the size of the R group because of the close proximity of the R group and the boryl group of the catalyst. Thus, we hypothesized that steric alteration of the imine substituent R from ^{t}Bu to ^{i}Pr to Me should enhance the meta selectivity further.

To test this hypothesis, borylations were performed with the isopropyl imine and methyl imine of benzaldehyde. Remarkably, a clear trend for the enhancement of the meta selectivity was observed as the imine substituent R was made smaller (Table 4). We reasoned that the enhanced meta selectivity (100% for R = Me) results from the reduced steric crowding, which facilitates the secondary interaction through the imine N atom and boryl B atom of the catalyst (**TS-2**). However, the question of mechanism is open to debate, and the detailed mechanism of each step remains to be ascertained.

Table 4. Effect of the Imine Substituent: Proof of the Hypothesis for Meta Borylation[a]



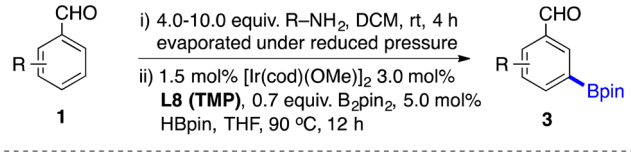
1a **3a**

#	R	meta/(para+ortho)[b]	mono/di	Conversion (%)[c]
1	^{t}Bu	66/34	93/07	78 (57)
2	^{i}Pr	84/16	90/10	73
3	Me	97/03	97/03	80 (73)[d]

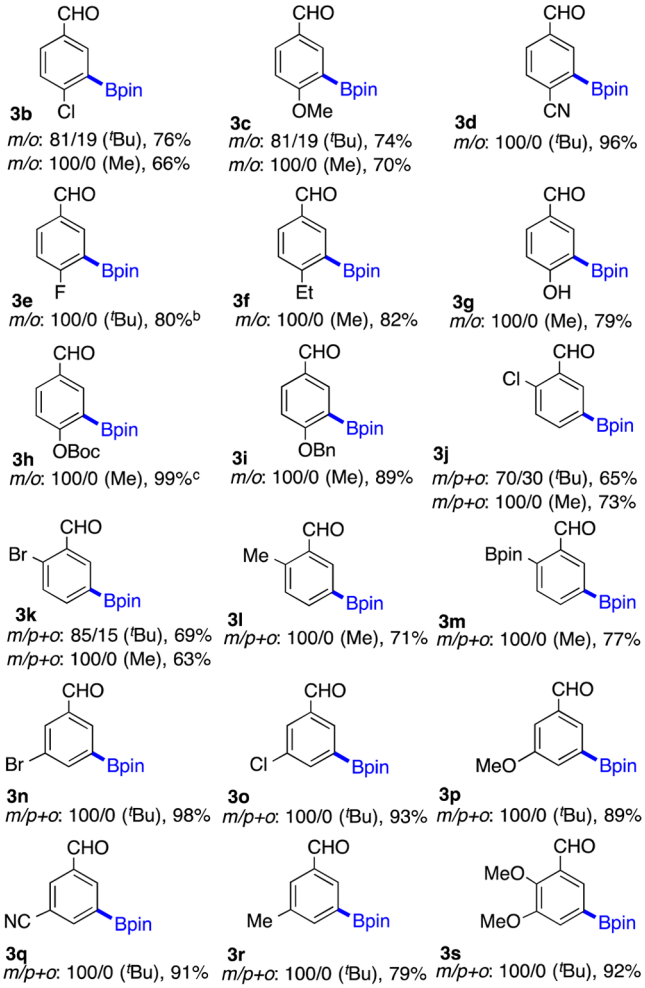
[a]Reactions were run with 1.0 mmol of substrate; see the SI for details. [b]GC ratios. [c]GC conversions, In GC/MS, no imine-borylated products were found; only aldehyde-borylated products were observed. [d]The isolated yield of the aldehyde-borylated product is given in parentheses.

Next, we explored the substrate scope for the meta borylation, and the results are summarized in Table 5. A wide range of substituents were well-tolerated under the borylation conditions, affording excellent meta selectivity and excellent isolated yields. For example, while 4-chlorobenzaldehyde gave 81/19 meta/ortho selectivity using *tert*-butylamine, it afforded 100% meta selectivity with methylamine as the protecting/directing group (entry **3b**). 4-Methoxybenzaldehyde gave 81/19 and 100/0 meta/ortho selectivity with *tert*-butylamine and methylamine, respectively (entry **3c**). Likewise, 4-cyano-, 4-fluoro-, 4-ethyl-, and 4-hydroxybenzaldehyde resulted the meta isomer as the sole product (entries **3d–g**). It deserves mention that even the use of a very bulky substituent such as an OBoc[23] or OBn group at the 4-position of the benzaldehyde afforded complete meta

Table 5. Meta Borylation of Substituted Benzaldehydes[a]



1 **3**



[a]Reactions were run with 1.0 mmol of substrate; for details, see the SI. Yields are for isolated meta-borylated aldehyde products after column chromatography. [b]2.0 mmol of substrate was used. [c]99% conversion.

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selectivity (entries **3h** and **3i**). Thus, these observations are consistent with the notion that an electrostatic interaction and a secondary interaction between the imine N atom and the boryl B atom of the catalyst control the meta selectivity.

On the other hand, 2-substituted substrates proved to be challenging because of several open reactive sites for C−H activation/borylation. For example, 2-Bpin-, 2-bromo-, 2-chloro-, and 2-methylbenzaldehyde could give mixtures of isomers. To our delight, they resulted complete meta selectivity (entries **3j**−**m**). For meta-substituted benzaldehydes, as expected, borylations occurred at the meta position, and no other borylations were observed (entries **3n**−**r**). Moreover, highly electron-rich 2,3-dimethoxybenzaldehyde proved to be an excellent meta-borylation substrate, giving an excellent yield (entry **3s**).

In summary, we have developed two complementary methods for the ortho- and meta-selective C−H bond activation/borylation of aromatic aldehydes that cannot be obtained with DoM or any other methodology. While the ortho borylation proceeds through directed C−H activation/borylation using *tert*-butylamine as the traceless protecting/directing group, the meta borylation undergoes through an electrostatic interaction and a secondary interaction between the ligand of the catalyst and the substrate. Both methods show very broad substrate scope and functional group tolerance. However, at this stage, we are not entirely certain about the working hypothesis for the meta-selective C−H activation/borylation, and further studies are underway, which will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b11683.

Full characterization, copies of all spectral data, and experimental procedures (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Diaz-Requejo, M. M.; Perez, P. J. *Chem. Rev.* **2008**, *108*, 3379. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.

(2) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890.

(3) (a) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206. (b) Hurst, T. E.; Macklin, T. K.; Becker, M.; Hartmann, E.; Kügel, W.; Parisienne-La Salle, J. C.; Batsanov, A. S.; Marder, T. B.; Snieckus, V. *Chem. - Eur. J.* **2010**, *16*, 8155.

(4) For a recent review of functional-group-directed borylation, see: Ros, A.; Fernandez, R.; Lassaletta, J. M. *Chem. Soc. Rev.* **2014**, *43*, 3229.

(5) (a) Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 7534. (b) Miyaura, N. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1535. (c) Kawamorita, S.; Ohmiya, H.; Hara, K.; Fukuoka, A.; Sawamura, M. *J. Am. Chem. Soc.* **2009**, *131*, 5058. (d) Kawamorita, S.; Ohmiya, H.; Sawamura, M. *J. Org. Chem.* **2010**, *75*, 3855. (e) Yamazaki, K.; Kawamorita, S.; Ohmiya, H.; Sawamura, M. *Org. Lett.* **2010**, *12*, 3978. (f) Ishiyama, T.; Isou, H.; Kikuchi, T.; Miyaura, N. *Chem. Commun.* **2010**, *46*, 159. (g) Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 134.

(6) Maleczka, R. E., Jr.; Shi, F.; Holmes, D.; Smith, M. R., III *J. Am. Chem. Soc.* **2003**, *125*, 7792.

(7) Murphy, J. M.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 15434.

(8) (a) Iverson, C. N.; Smith, M. R., III *J. Am. Chem. Soc.* **1999**, *121*, 7696. (b) Cho, J. Y.; Iverson, C. N.; Smith, M. R., III *J. Am. Chem. Soc.* **2000**, *122*, 12868. (c) Cho, J. Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E., Jr.; Smith, M. R., III *Science* **2002**, *295*, 305. (d) Chotana, G. A.; Rak, M. A.; Smith, M. R., III *J. Am. Chem. Soc.* **2005**, *127*, 10539.

(9) For borylation of aromatic ketones, see: Itoh, H.; Kikuchi, T.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **2011**, *40*, 1007.

(10) For secondary-interaction-directed meta-selective C−H borylation, see: Kuninobu, Y.; Ida, H.; Nishi, M.; Kanai, M. *Nat. Chem.* **2015**, *7*, 712.

(11) (a) Tomohiro, K.; Hideto, F.; Katsumi, K.; Shigeru, K. PCT Int. Appl. WO 2010110400, 2010. (b) Takeshi, K.; Hiroshi, N.; Tomoko, I.; Mitsukane, Y.; Kensei, Y. Jpn. Kokai Tokkyo Koho JP 2010173974, 2010.

(12) Matteson, D. S.; Talbot, M. L. *J. Am. Chem. Soc.* **1967**, *89*, 1123.

(13) For Ir-catalyzed nitrogen-directed ortho borylation, see: (a) Ros, A.; Estepa, B.; López-Rodríguez, R.; Alvarez, E.; Fernández, R.; Lassaletta, J. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 11724. (b) López-Rodríguez, R.; Ros, A.; Fernández, R.; Lassaletta, J. M. *J. Org. Chem.* **2012**, *77*, 9915. (c) Ros, A.; López-Rodríguez, R.; Estepa, B.; Àlvarez, E.; Fernández, R.; Lassaletta, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 4573.

(14) For Rh-catalyzed nitrogen-directed ortho borylation, see: Kawamorita, S.; Miyazaki, T.; Ohmiya, H.; Iwai, T.; Sawamura, M. *J. Am. Chem. Soc.* **2011**, *133*, 19310.

(15) For aromatic imine-directed ortho borylation, see: Sasaki, I.; Amou, T.; Ito, H.; Ishiyama, T. *Org. Biomol. Chem.* **2014**, *12*, 2041.

(16) For imine-directed ortho silylation, see: (a) Choi, G.; Tsurugi, H.; Mashima, K. *J. Am. Chem. Soc.* **2013**, *135*, 13149. (b) Williams, N. A.; Uchimaru, Y.; Tanaka, M. *Dalton Trans.* **2003**, 236.

(17) *o*-BpinC_6H_4CHO can easily be distinguished by the ∼0.6 ppm downfield shift of its CHO resonance in ^{1}H NMR spectra due to hydrogen bonding to a Bpin O.

(18) The imine-borylated products can be seen in the crude ^{1}H NMR spectra (see the SI for details). We assumed that in the GC/MS, the imine-borylated products are hydrolyzed. Likewise, the products are hydrolyzed during silica gel column chromatography.

(19) The mechanism of the ortho C−H bond activation/borylation of aldehydes via in situ-generated imines is related to the analogous ortho borylation of hydrazones reported by Fernández-Lassaletta.[13a]

(20) (a) Das, S.; Incarito, C. D.; Crabtree, R. H.; Brudvig, G. W. *Science* **2006**, *312*, 1941. (b) Leung, D. H.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2006**, *128*, 9781. (c) Breslow, R.; Zhang, X.; Huang, Y. *J. Am. Chem. Soc.* **1997**, *119*, 4535.

(21) For encapsulation of iridium species facilitated via an electrostatic interaction, see ref 20b.

(22) For an example of H-bonding of imines, see: (a) Ligtenbarg, A. G.; Hage, R.; Meetsma, A.; Feringa, B. L. *J. Chem. Soc., Perkin Trans. 2* **1999**, 807. For H-bond-directed ortho borylation, see: (b) Roosen, P. C.; Kallepalli, V. A.; Chattopadhyay, B.; Singleton, D. A.; Maleczka, R. E., Jr.; Smith, M. R., III *J. Am. Chem. Soc.* **2012**, *134*, 11350.

(23) Isolation of **3h** failed because of elimination of the Boc group during silica gel column chromatography. **3g** was isolated instead.

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